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14. ABSTRACT

To catalog the side effects of 2.4 atmospheres absolute (atm abs) hyperbaric oxygen (HBO2) *vs.* sham on post-concussion symptoms in military service members with combat-related, mild traumatic brain injury (TBI). Fifty subjects diagnosed with TBI were randomized to either a sham (1.3 atm abs breathing air) or treatment (2.4 atm abs breathing 100% oxygen) hyperbaric profile. Forty-eight subjects completed 30 exposures. Medical events during hyperbaric exposures were separately annotated by medical staff and chamber operators. After the blind was broken, events were segregated into the exposure groups. These side effects were observed as rate (sham/treatment): ear block (ear barotrauma) 5.51% (1.09%/5.91%), sinus squeeze 0.14% (0.0%/0.27%), and confinement anxiety 0.27% (0.27%/0.27%). Other conditions that occurred included: headache 0.61% (0.68%/0.54%); nausea 0.2% (0.14%/0.27%); numbness 0.07% (0%/0.13%); heartburn 0.07% (0.14%/0%); musculoskeletal chest pain 0.07% (0%/0.13%); latex allergy 0.07% (0.14%/0%); and hypertension 0.07% (0.14%/0%). This study demonstrated no major adverse events, such as pulmonary barotraumas, pulmonary edema or seizure. Given the infrequent, mild side effect profile, the authors feel the study demonstrated that hyperbaric oxygen therapy (HBO2T) was safe at a relatively high treatment pressure in TBI subjects, and these data can be used to evaluate the risk/benefit calculation when deciding to utilize HBO2T for treatment of various diseases in the TBI population.

15. SUBJECT TERMS

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Hyperbaric side effects in a traumatic brain injury randomized clinical trial

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ABSTRACT

Objective: To catalog the side effects of 2.4 atmospheres absolute (atm abs) hyperbaric oxygen (HBO_2) *vs*. sham on post-concussion symptoms in military service members with combat-related, mild traumatic brain injury (TBI).

Methods: Fifty subjects diagnosed with TBI were randomized to either a sham (1.3 atm abs breathing air) or treatment (2.4 atm abs breathing 100% oxygen) hyperbaric profile. Forty-eight subjects completed 30 exposures. Medical events during hyperbaric exposures were separately annotated by medical staff and chamber operators. After the blind was broken, events were segregated into the exposure groups.

Results: These side effects were observed as rate (sham/treatment): ear block (ear barotrauma) 5.51% (1.09%/5.91%), sinus squeeze 0.14% (0.0%/0.27%), and confinement anxiety 0.27% (0.27%/0.27%). Other conditions that occurred included: headache 0.61% (0.68%/0.54%); nausea 0.2% (0.14%/0.27%); numbness 0.07% (0%/0.13%); heartburn 0.07% (0.14%/0%); musculoskeletal chest pain 0.07% (0%/0.13%); latex allergy 0.07% (0.14%/0%); and hypertension 0.07% (0.14%/0%).

Conclusion: This study demonstrated no major adverse events, such as pulmonary barotraumas, pulmonary edema or seizure. Given the infrequent, mild side effect profile, the authors feel the study demonstrated that hyperbaric oxygen therapy (HBO_2T) was safe at a relatively high treatment pressure in TBI subjects, and these data can be used to evaluate the risk/benefit calculation when deciding to utilize HBO_2T for treatment of various diseases in the TBI population.

INTRODUCTION

The use of hyperbaric oxygen (HBO_2) in neurologic diseases has long been a hotbed of research and has yielded mixed results. An increase in the frequency of United States military traumatic brain injury (TBI) patients from the wars in Afghanistan and Iraq resulted in the Congressionally Directed Medical Research Programs' Psychological Health and Traumatic Brain Injury (CDMRP PH/TBI) Research Program. It was established in 2007 in response to U.S. Troop Readiness, Veterans' Care, Katrina Recovery, and Iraq Accountability Appropriations Act, Public Law 110-28. Anecdotal reports purporting the benefits of hyperbaric oxygen for treating traumatic brain injury precipitated the development of the United States Air Force (USAF) HBO-TBI study in 2007. Much of the study design was based on the Agency for Healthcare Research and Quality's (AHRQ) Evidence Report/Technology Assessment, Number 85, "Hyperbaric Oxygen Therapy for Brain Injury, Cerebral Palsy, and Stroke" [1]. The report recognized the early case reports by Dr. Gaylan Rockswold using hyperbaric oxygen for acute severe traumatic brain injury. AHRQ also stated, "The most important gap in the evidence is a lack of a good quality time-series study or controlled trial of the effects of HBOT on cognition, memory, and functional status in patients with deficits due to mild and moderate chronic TBI."

AHRQ made recommendations for future research for hyperbaric oxygen and its use for TBI, suggesting strategies to overcome barriers. One barrier was a lack of agreement on the dosage of HBO_2 and the duration of treatment. Unlike oral or intravenous medications that are measured in milligrams, individual dosages of hyperbaric oxygen are measured in partial pressures of oxygen multiplied by time. The partial pressure is calculated by multiplying the amount of oxygen breathed

(up to 100%) times the pressure, usually described in atmospheres absolute (atm abs), with one atmosphere being what we experience at sea level and each additional atmosphere pressure equivalent to 33 feet of sea water (fsw). The dose chosen is then repeated daily until a total dose is achieved as expressed by the numbers of sessions or treatments. Nearly all of the pressures used in the anecdotal reports for treating TBI involved using 100% oxygen at 1.5 atm abs, with duration of one hour per session for a total of 40 sessions per series. AHRQ recommended future studies to look at various doses and treatment duration.

A second barrier was the lack of independent, reliable data on the frequency and severity of adverse events. The AHRQ's text regarding this barrier follows:

Uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT. The case against HBOT is based on the reasoning that, because HBOT may be harmful, it must be held to the highest standard of proof. A corollary is that, if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its efficacy can be lowered.

This reasoning is consistent with the views of most clinicians and with the theoretical underpinnings of rational decision- making (i.e., utility theory). Consider a treatment that has been proven to be harmless and without cost. If there is a 1 percent chance that the treatment works, a rational decision maker would try it – there is a potential gain and no potential loss. On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it.

The objective of the USAF HBO-TBI study was to track the known potential treatment complications between two hyperbaric exposure groups, one sham and the other a treatment exposure. As many general trauma patients who also have a TBI history are treated with hyperbaric oxygen using higher pressure profiles, risk-benefit considerations are of importance.

METHODS

The study "Treatment of Moderate to Mild Cognitive Dysfunction Caused by Traumatic Brain Injury with Hyperbaric Oxygen Therapy (HBOT)" was submitted through the then Wilford Hall Medical Center Institutional Review Board (IRB). IRB approval was granted in August 2007 and was consistent with the Declaration of Helsinki, CFR Part 50 "Protection of Human Subjects," and Air Force Instruction 40-402 "Protection of Human Subjects in Biomedical and Behavioral Research."

Fifty subjects diagnosed with traumatic brain injury and having deficits in cognitive function were identified by neurologists. All patients included in the study suffered a TBI up to six years prior to the start of treatment. There were 48 males and two females. The range of subject ages was from 20 to 51 years of age with a mean of 28.32 years and a standard deviation (SD) of 7.7 years. The subjects were randomly entered into one of two groups, a sham group and a treatment group. Each group had a total of 25 subjects comprising 24 males and one female. The age range was 21 to 46 years in the sham group with a mean of 28.4 years and an SD of 7.4 years. The age range was 20 to 51 years old in the treatment group with a mean of 28.3 years and an SD of 8.1 years. There was one withdrawal from each group.

Hyperbaric exposure profiles

The original protocol submitted to the CDMRP in 2007 was comprehensive and had four exposure (dosage) groups (sham, 1.7 atm abs, 2.4 atm abs and 3.0 atm abs). At the initial review, the research panel recommended that a pilot study be done first; the panel felt the original proposal was "too aggressive" and the researchers had few publications, thus not worthy of the grant. The resultant pilot study reported here continued the AHRQ recommendations to address dose response data and collect information regarding adverse events. The revised study bracketed the anecdotal pressure of 1.5 atm abs with two exposure groups: the treatment group using 100% oxygen (O_2) at 2.4 atm abs for 90 minutes (a standard wound treatment pressure and duration) and a sham or control group breathing air (21% O_2) for 90 minutes at 1.3 atm abs (about the pressure at 11 fsw). The pressure of 2.4 atm abs was chosen due to its routine clinical use but also to evaluate the safety and side effect aspects at this pressure in the TBI population. Exposures were done in a multiplace chamber with the breathing medium delivered using an oxygen treatment hood (Amron International Inc., Vista, Calif.) once the exposure pressure was reached. The chamber was dedicated to the research study with no interference by clinical activities. Exposures were done on weekdays only. Subjects completed five exposures followed by one day given to complete other aspects of the study. The cycle was repeated for a total of 30 exposures.

The 2.4-atm abs treatment exposures had a seven-minute descent to 45 fsw equivalent with 90 minutes of

TABLE 1 – ***Side effect rates as percentage of events per exposures***

SIDE EFFECT	Events	# of subjects	Overall rate	# of subjects	Sham rate	# of subjects	Treatment rate
Ear barotrauma	52	14	3.51	4	1.09	10	5.91
Sinus squeeze	2	1	0.14	0	0	1	0.27
Confinement anxiety	4	2	0.24	1	0.27	1	0.27
Progressive myopia	0	0	0	0	0	0	0
Cataract	0	0	0	0	0	0	0
Pulmonary barotrauma	0	0	0	0	0	0	0
Pulmonary edema	0	0	0	0	0	0	0
Seizure	0	0	0 0	0	0 0	0	0 0
Headache	9	7	0.61	3	0.68	4	0.54
Nausea	3	3	0.2	1	0.14	2	0.27
Numbness	1	1	0.07	0	0	1	0.13
Heartburn	1	1	0.07	1	0.14	0	0
Latex allergy	1	1	0.07	1	0.14	0	0
Chest pain	1	1	0.07	0	0	1	0.13
Hypertension	1	1	0.07	1	0.14	0	0

oxygen broken into three 30-minute periods interspersed by breathing air for a 10-minute period by removing the hood from the subject's head. This "air break" is given to reduce the risk of seizure, a known side effect of hyperbaric oxygen that will be discussed later. At the completion of the third 30-minute oxygen breathing period, the hood was removed and the chamber depressurized with a 10-minute ascent to surface.

The sham pressure of 1.3 atm abs was used consistent with several prior studies. Van Ophoven [2] used a treatment chamber pressure of 2.4 atm abs with 100% O_2 with a sham of 1.3 atm abs breathing normal air, each for 90 minutes. Nighoghossian [3] compared 1.5 atm abs (100% O_2 for 40 minutes) to 40 minutes of air at 1.2 atm abs. Rusyniak [4] treated stroke patients at 2.5 atm abs breathing 100% O_2 with a control of 1.14 atm abs breathing 100% O_2. Clarke [5] evaluated blinding between 2.0 atm abs and 1.3 atm abs with a drift to 1.1 atm abs, demonstrating subject validation of the technique.

The 1.3-atm abs sham exposure consisted of a seven-minute descent to 11 fsw equivalent with the 90 minutes of air broken into three 30-minute periods interspersed by breathing air for a 10-minute period by removing the hood from the subject's head. This was done to make the two profiles as similar as possible. Upon reaching 1.3 atm abs, the chamber was allowed to slowly drift over a 10-minute period to 6 fsw (1.1 atm abs) as part of routine chamber venting. The pressure remained at this level until the completion of the third breathing period, at which time there was an ascent to surface over 10 minutes.

Side effects and complications

Side effects defined by the Undersea and Hyperbaric Medical Society (UHMS) were tracked throughout the study *(see Table 1, above)*. Medical monitors interviewed each subject for interval medical history from the previous exposure, checked tympanic membranes and auscultated the heart and lungs. Any medical issue was addressed by the medical monitor before the exposure as well as after the exposure, as needed. The medical monitor annotated findings on a subject daily log of operations. In addition, any medical or physical complaint experienced by subjects during the hyperbaric exposure was annotated in the "dive record" by the chamber operator.

After the blind was broken, side effects and complications were segregated into the respective exposure group and compared between the daily medical monitor log and the dive record entries. From all subjects, there

were 1,480 pressurization events including nine make-up exposures required when a subject was removed from the chamber. The number of pressurizations in the sham group was 736 and in the treatment group 744. These numbers were used as the denominator for determining the rate of individual side effects observed in each group.

Blinding

The study was written as a single blind study. However, a decision was made to operate the study as a double blind. Each hyperbaric exposure was run by a research crew consisting of the crew chief, chamber operator, inside attendant and the medical monitor. The crew chief is responsible for the safety and mechanical aspects of the chamber. The chamber operator controls the pressurization, venting and depressurization of the chamber. The inside observer attends to the subjects, dons and doffs the hoods as required, and is in communication with the chamber operator at all times. The medical monitor authorizes chamber pressurization and determines any medical interventions needed throughout the hyperbaric exposure.

Obviously, the chamber operators and, most likely, the inside attendants were aware of the exposure profile, but the medical monitors were not. Nondisclosure agreements were signed by each of the research crew prior to starting compression. It specified that no information regarding the exposure pressure would be discussed with anyone including members of the research crew, the research coordinator, subjects or any inquiries from outside the research area.

The inside observers were instructed to perform a Valsalva maneuver every 10-30 seconds during chamber pressurization. The inside observers also breathed oxygen from their mask three times during every exposure to prophylax against decompression sickness regardless of exposure profile. The chamber operator would use percentage of depth achieved, if asked by the medical monitor for issues such as ear blocks. Venting of the chamber by the operator was also done in both exposure groups to create similar temperature and noise levels. In addition, all clocks and pressure gauges were removed from inside the chamber, and no watches or electronics were allowed inside the chamber.

Randomization to the exposure groups was done using a computer-generated number assignment (randomizer.org©). The consent agreement included a discussion of sham and experimental exposures, and the subjects were informed they may be assigned to either group. During consent, subjects were told the breathing mixture within the hood could be either oxygen or air. Subjects were assigned specific places with corresponding gas/hood assemblies in the chamber. As part of the precompression checklist, subjects were identified by their subject number, their assigned position and the "breathing gas mixture" confirmed by the inside observer orally where the subjects could hear. However, all 1.3-atm abs exposures used air and all 2.4-atm abs exposures used 100% O_2.

At the conclusion of the data collection, but prior to breaking the blind, a questionnaire was sent to the subjects asking:

Do you feel that you were in
(1) the treatment group,
(2) the placebo group, or
(3) have no idea?

Analysis of data was performed at the completion of all exposures and after the blind was broken.

RESULTS

In the study as a whole, ear block (ear barotrauma), sinus block and confinement anxiety *(Table 1)* were the only side effects observed. As all medical issues were tracked, other conditions and rates that occurred included headache (0.61%), nausea (0.2%), numbness (0.07%), heartburn (0.07%), musculoskeletal chest pain (0.07%), latex allergy (0.07%) and hypertension (0.07%). The rates are expressed as the number of events per the number of exposures as a total or in the individual groups. In addition, Table 1 also includes the raw number of subjects who experienced events, as one individual may have had more than one event in a category.

Ear blocks were defined as any time a subject was unable to equalize middle ear pressure during descent and required the pressurization to be stopped. Ear blocks were the most common side effect and paralleled what is seen clinically, with a total of 52 events. Unresolved ear block required removal from the chamber seven times, all from the treatment group. The overall rate of ear blocks was 3.51%, which compares with 2% [6] in the clinical population. The sham group had a 1.09% rate and the treatment group a 5.91% rate. Of the 52 events, 33 occurred at 11 fsw or shallower (63%), which was the maximum depth of the sham exposure. Using the TEED 0-5 scale, there were eight events that were diagnosed with a TEED 2. All others were either 0 or 1. Sinus squeeze events were observed only in the treatment group. Confinement anxiety occurred equally between the groups, with two events each. Progressive myopia (defined as worsening by two or more Snellen lines), cataracts, pulmonary barotraumas or edema, or seizure were not reported.

Other adverse effects reported included nine headaches that occurred while inside the chamber; three cases of nausea; one case each of numbness, heartburn, latex allergy and chest pain; and one subject whose blood pressure gradually increased over the exposure series.

Only 16 of the 50 subjects (32%) responded to the blinding questionnaire regarding their perception as to which group they were in. One responded affirmatively to being in the treatment group, four thought they were in the sham group, and 11 did not know. Of those who guessed their group, two guessed correctly and three guessed incorrectly.

DISCUSSION

Side effects and complications

Barotrauma: In analyzing subjects who had ear block events, there were only 14 individuals (27% of the subjects) who were responsible for the 52 events. Ten were assigned to the treatment (Rx) group, and four were in the sham group. In allowing two events to occur from a "training" perspective, there were only five individuals (10%) who had more than two events, four in the treatment group and one in the sham group. Of these four treatment group subjects, two had allergic rhinitis, one had an upper respiratory infection (URI) that also kept him from exposures for approximately one week, and one had a nasal septal deviation. Interventions for ear and sinus blocks in both groups included educating all subjects in various equalization techniques, reducing the pressure (bouncing) of the chamber to allow better equalization, decongestant sprays or medications, reduced pressurization rate and Otovent use.

Otovent was used in three of the four multiple block subjects after it appeared they had difficulty equalizing pressure (7-8 blocks early in the series). None of them required removal from the chamber after the Otovent was initiated. The URI subject did not require an Otovent. The sham subject responded to chamber bounce and decongestant spray. As no severe barotrauma (TEED 3 or greater) was experienced in the study, it increases the argument for typical hyperbaric oxygen therapy as being safe. One of the allergic rhinitis subjects was responsible for the two sinus blocks that occurred two days apart. These were reverse blocks during ascent that resolved spontaneously without further problems.

Anxiety: Anxiety occurred twice in one subject in each group. Both responded to taking off the hood until they felt better and then resuming the exposure to completion. The treatment subject opted to breath via aviator's mask instead of the hood after the second episode and continued without anxiety for the remainder of his exposures. The sham subject experienced anxiety during his third week in the treatment series. He had been taking clonazepam for anxiety as needed prior to consenting as a subject. He started taking it before hyperbaric exposures on days he felt anxious and tolerated the exposures well thereafter.

TABLE 2 – ***Visual acuity changes post series and at 6-week follow-up***

Snellen[1]	Post series R eye	Post series L eye	Total	Post 6 wk R eye	Post 6 wk L eye	Total
-1	2	3	5	1	2	3
-1	4	3	7	2	4	6
0	13	8	21	9	9	18
0	12	14	26	9	10	19
1	5	8	13	9	8	17
1	7	5	12	8	6	14
2	3	4	7	3	4	7
2	1	1	2	5	3	8
3	0	0	0	1	0	1
3	0	0	0	0	0	0
			SHAM			
Total	23	23	46	23	23	46
Total	24	23	47	24	23	47
			TREATMENT			

[1] Positive Snellen lines (1-3) demonstrate improvement in vision whereas negative (-1) indicates worsening by one Snellen line. Zero indicates no change.

Visual effects: Progressive myopia did not occur in any of the subjects. Progressive myopia of hyperbaric oxygen exposure is attributed to an alteration in the lens shape with unknown reason [7]. In a retrospective study of 88 patients, most of whom underwent 2.0-atm abs treatments, Dedi [8] found there was a slight trend toward greater loss of acuity than gain in acuity over treatment time. In 20 2.4-atm abs treatments in 52 patients with an average age of 62.9 years, Smerz [9] demonstrated visual changes, predominantly myopia, were common in this particular study population. Finally, 14 patients (average age 54.1 years) treated at 2.4 atm abs (29.6 average sessions) in a report by Churchill [10] showed myopia in 78%.

In this study, there were 93 eyes with visual acuity data *(Table 2, above)*. The number was decreased from

100 due to the two withdrawals, one subject who had one blind eye and the first subject who did not receive a baseline acuity. There were 12 eyes (five sham/seven Rx) with a one-Snellen-line decrease at the end of the series and nine eyes (three sham/six Rx) at the six-week follow-up point. However, there were 34 (36%) eyes that improved by greater than one Snellen line post series and 47 (50%) at the six-week follow-up. The respective changes at these timelines for the groups were 20 sham/14 Rx post series and 25 sham/22 Rx at the six-week follow-up. More interesting was the two-Snellen-line improvement in nine eyes (seven sham/two Rx) post series and 15 (seven sham/eight Rx) at the six-week follow-up point. One sham eye had a three Snellen line improvement at the 6-week follow-up point. The age range in these subjects was 22-46 years (two older than 40) in the sham group and 20-51 years (two older than 40) in the treatment group. All baseline acuities were 20/40 [3] or better, with the majority [10] starting off 20/20.

Kinney [11] showed no decrements in visual acuity or in the size of the field of view in four subjects who lived in a chamber pressurized at either 50 feet or 60 feet. However, in looking at Kinney's raw data, three subjects remained at baseline, but one subject at the 50-foot level improved vision in his eyes by two to three levels. Just as there is no good explanation as to why hyperbaric oxygen may result in myopia, improvement in these hyperbaric exposures cannot be explained. Considering current research (references above) and the observed changes in this study, it may be both an oxygen effect as well as pressure effect. More research in this area could be beneficial, particularly in military occupations in which better visual acuity beyond 20/20 is desirable, such as infantry, aviation and special operations.

Seizure: There were no seizure events in the study despite the prediction voiced at the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury "Consensus Conference for Hyperbaric Oxygen Therapy in Traumatic Brain Injury" in Alexandria, Va., 5-6 December 2008 (Harch P. Personal communication; 2008). The concern was that HBO_2T 2.4 is harmful to the brain, and the brain "shuts off" oxygen at that level to protect itself to avoid the induced seizures seen at this oxygen dose. In acute severe TBI, Rockswold [12] treated 22 patients at 1.5 atm abs where critical brain tissue oxygen levels were achieved without biochemical evidence of oxygen toxicity and no seizure. Lin's study of 22 acute moderate to severe TBI patients treated at 2 atm abs had two subjects who had a seizure [13]. It should be noted, however, that both subjects resumed the hyperbaric therapy without further episodes but were eliminated from the statistical analysis. It is prudent to believe that in acute severe TBI, the brain is in active recovery and more sensitive to oxygen loads. Rockswold's study above may pave the way for future research to see if the critical level of brain oxygen tissue partial pressure (200 mmHg) can be achieved in >50% [14] of acute severe TBI patients using 2.0 atm abs or higher with continued biochemical evidence of no oxygen toxicity.

Seizures have been seen in the routine treatment of neurological decompression sickness (DCS) and carbon monoxide poisoning, both acute neurological events, as well as daily hyperbaric oxygen treatments for all UHMS indications in patients who may have had previous brain insults. The rate of seizures overall clinically ranges from 0.01% to 0.03% in day-to-day operations but as high 1.8% when treating carbon monoxide poisoning [15]. Acute severe TBI may be a different presentation than seen in this study's chronic mild TBI population. Realistically, chronic TBI patients have had some recovery from a healing perspective. Although this study did not have any seizure events, the true seizure rate for this subset likely lies between 0.01% and 1.8% referenced above but can only be determined after meta-analysis of this and future published studies.

Headache: Thirty subjects had a history of headaches prior to the study, a common symptom in TBI patients. Some of these subjects had a low-grade headache 24 hours a day. Consequently, the nine events reported were in subjects whose pain level increased during the exposure if they were already experiencing headache upon starting compression or the development of a new headache while in the chamber. Most of these headaches responded to either ibuprofen or acetaminophen or resolved spontaneously.

There was one subject who did not have a headache history who developed recurrent headaches on multiple dives. He withdrew from the study for personal reasons. This subject had retained shrapnel in his brain near the pineal gland. A computed tomography (CT) scan impression that was reviewed prior to consent demonstrated this as well as post open reduction and internal fixation of the left infraorbital comminuted fracture without evidence of hardware complication. His ability to equalize ear pressure without difficulty was confirmed by his base physician prior to consent. Upon closer review of the CT report, a lobulated mucosal thickening was reported within the right maxillary sinus and right sphenoid sinus. The acute migraine headache-like symptoms were consistent, particularly with those seen with sphenoid sinusitis. A possible explanation was a

sinus squeeze in the sphenoid sinus, perhaps as a ball valve phenomenon seen rarely in aircrew and divers. As the symptom did not present as a traditional sinus squeeze, it was relegated to the actual complaint of a headache. The subject was in the sham exposure group.

Nausea/heartburn: The nausea that was registered was attributed by two of the subjects to food, and the third developed acute gastroenteritis the evening of the event. The heartburn, also attributed to food by the subject, was resolved with antacids. Nausea is a well-recognized pre-monitory sign of central nervous system oxygen toxicity. However, all three events occurred 42 minutes or less into the exposures, essentially after only one breathing period. Given the resultant histories, it is very unlikely oxygen toxicity is a concern.

Latex allergy: One subject developed neck irritation but did not have a known latex allergy. It quickly resolved after a non-latex hood ring seal was used.

Numbness: One subject developed numbness in his right arm and hand during ascent on his first compression. The symptoms spontaneously resolved by the time the chamber reached surface. No recurrence of the symptoms occurred. DCS in the subjects was likely not a concern, as in the treatment profile the subjects had adequate denitrogenation, and the sham group was at a depth that would not put the subject at risk for DCS. Air embolism was a possibility but unlikely due to the slow ascent, allowing air exchange in the lungs and no upper respiratory symptoms. Hyperventilation was also a possibility due to the new experience. The subject was in the treatment group.

Chest pain *(musculoskeletal)*: One subject developed musculoskeletal discomfort secondary to neck ring pressure to the left 4th-5th rib intercostal areas while the subject fell asleep during the breathing periods. Upon exam, there was point tenderness on palpation. The discomfort resolved over two days.

Hypertension: One subject arrived with a baseline blood pressure of 139/96. The pressure gradually increased through the first four weeks, with the highest blood pressure being 162/106. This resulted in an internal medicine consult. The subject was started on blood pressure medication and was still elevated at 147/94 at the six-week follow-up. The subject was in the sham exposure group.

Blinding

The sham profile choice was determined by evaluating the published works cited above. A hybrid of the van Ophoven and Clarke profiles was created. It was felt that the Clarke profile had the advantages of minimizing oxygen partial pressure within the sham group and thus minimizing any resultant "treatment" effect as well as validating the blinding. This study had a treatment pressure of 2.4 atm abs, as in the van Ophoven study. The disadvantage was the drift from 1.3 atm abs to 1.1 atm abs, as the study could have left the pressure just at 1.3 atm abs and accepted the higher oxygen partial pressure and the subsequent treatment effect.

Choosing this profile required a more active driving of the chamber by the operator to minimize any detection of pressure changes by the subjects. The chamber operators underwent additional training and "dry runs" before consenting subjects to achieve the sham intent, *i.e.*, the same noise, temperature and pressure effects experienced by the subjects in both exposure groups. Although the post-exposure survey did not obtain the desired number of responses, those who did respond predominantly had no idea which exposure group they were in (69%), and those who guessed were only 40% correct. It is felt that the blind was successful for the study.

CONCLUSION

This single-blinded, randomized, controlled trial was conducted to help determine the potential of hyperbaric oxygen as treatment for traumatic brain injury. A secondary goal was to follow the AHRQ recommendations to produce independent, reliable data on the frequency and severity of adverse events by tracking not only known side effects but also monitoring subjects for any medical conditions that occurred throughout the hyperbaric experience. This was done in both exposure groups. The treatment pressure level used a standard clinical profile (2.4 atm abs) compared to the anecdotal treatment pressure of 1.5 atm abs

This study demonstrated sham pressure of 1.3 atm abs was used consistent with several prior studies. Van Ophoven [2] used a treatment chamber pressure of 2.4 atm abs with 100% O_2 with a sham of 1.3 atm abs breathing normal air, each for 90 minutes. Nighoghossian [3] compared 1.5 atm abs (100% O2 for 40 minutes) to 40 minutes of air at 1.2 atm abs Rusyniak [4] treated stroke patients at 2.5 atm abs breathing 100% O_2 with a control of 1.14 atm abs breathing 100% O_2. Clarke [5] evaluated blinding between 2.0 atm abs and 1.3 atm abs with a drift to 1.1 atm abs, demonstrating subject validation of the technique, such as pulmonary barotraumas, pulmonary edema or seizure. It did have subjects who manifested known mild and reversible side effects such as ear barotrauma (ear block), sinus barotraumas (sinus

squeeze) and confinement anxiety, but these side effects were infrequent and caused no discernible lasting injury.

Other incidental medical conditions also occurred: headache, numbness, heartburn, latex allergy, chest pain (musculoskeletal) and hypertension over time. Given the infrequent, mild side effect profile, the authors feel that the study demonstrated that HBO_2T was safe at a relatively high treatment pressure in traumatic brain injury subjects and that, subsequently, these data can be used to alter the risk/benefit calculation when deciding whether to utilize HBO_2T in the treatment of various diseases in the TBI population. Per the AHRQ, the standard of proof of HBO_2T efficacy should be lowered.

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